Acknowledgements: The NAS report *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects* represents the efforts of the National Research Council's Committee on Passive Smoking. Committee members include:

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This paper relies heavily on references cited in *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects* (National Academy Press, Washington D.C., 1986) and *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General* (U.S. Department of Health and Human Services DHHS (CDC) 87-8398, 1986).

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Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?

P. N. Lee

Summary

Combined evidence from at least 15 epidemiological cohort and case-control studies appears to indicate non-smokers married to smokers have a risk of lung cancer 30%–40% higher than that of non-smokers married to non-smokers. This increase is surprisingly large, given the very low level of exposure to smoke constituents of non-smokers compared with that of smokers. The possibility that it results wholly or in part from bias, rather than as a direct effect of exposure to environmental tobacco smoke (ETS), must be considered seriously. Weaknesses of much of epidemiological evidence and the various possible sources of bias are discussed in detail.

One serious potential source of bias arises if even a small proportion of smokers are misclassified as non-smokers. Data from a series of studies specifically designed to determine accuracy of statements on current smoking habits (by salivary cotinine measurements) and on past smoking habits by repeated questionnaires) suggests that such misclassification might cause bias large enough to explain a major part, and perhaps all, of the apparent increase in lung cancer risk related to spouse smoking. Whilst evidence from a detailed review of the available literature on misclassification of smoking habits, is consistent with this view, there is a need for more research on this issue. Future epidemiological studies on passive smoking and lung cancer need to obtain more objective and reliable information on the subject's smoking habits and exposure to ETS. Bias can also arise if positive studies are more likely to be reported than negative studies and research is needed to attempt to estimate the extent of this bias.

Data currently available do not permit reliable conclusions to be drawn concerning the relationship of ETS exposure to lung cancer risk.

The Association

Since the early studies of Hirayama (1981) and Trichopoulos et al. (1981) reporting that never smokers married to smokers have a higher risk of lung cancer than those married to non-smokers, further epidemiological evidence has accumulated. Table 1 summarizes evidence from 16 published studies, 1–3 being prospective studies and 4–16 case-control studies. Wald et al. (1986), based on results from studies 1–13, reported an overall significant relative risk of 1.35, with 95% confidence limits of 1.19–1.54. This estimate is in broad agreement with other estimates of 1.30 (Lee 1984), 1.41 (Wells 1986) and 1.2–1.5 (Doll 1986). It would not be materially affected by including results from studies 14–16 of Table 1 since they are all small, and have relative risks that vary either side of the average.

While the overall evidence, which is based on a total of almost 1,200 lung cancer deaths in never smokers, predominantly in females, suggests a statistically significant

H. Kasuga (Ed.) Indoor Air Quality
© Springer-Verlag, Berlin Heidelberg 1990

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Table 1. Summary of epidemiological studies of risk of lung cancer in never smokers in relation to environmental tobacco smoke exposure

Study number	Authors	Study location	Sex	Number of lung cancers[a]	Relative risk	Significance[b]
1	Hirayama (1981, 1984)	Japan	F	163	1.63	Yes
			M	64	2.25	Yes
2	Garfinkel (1981)	USA	F	153	1.17	No
3	Gillis et al. (1984)	Scotland	F	8	1.00	No
			M	6	3.25	No
4	Trichopoulos et al. (1981, 1983)	Greece	F	77	2.11	Yes
5	Chan and Fung (1982)	Hong Kong	F	84	0.75	No
6	Correa et al. (1983)	USA	F	22	2.07	(Yes)
			M	8	2.00	No
7	Buffler et al. (1984)	USA	F	41	0.78	No
			M	11	0.52	No
8	Kabat and Wynder (1984)	USA	F	24	0.79	No
			M	12	1.00	No
9	Koo et al. (1984, 1987)	Hong Kong	F	88	1.64	No
10	Garfinkel et al. (1985)	USA	F	134	1.31	(Yes)
11	Akiba et al. (1986)	Japan	F	94	1.50	No
			M	19	1.80	No
12	Lee et al. (1986)	England	F	32	1.00	No
			M	15	1.30	No
13	Pershagen et al. (1987)	Sweden	F	67	1.20	No
14	Wu et al. (1985)	USA	F	29	1.20	No
15	Ziegler (in Delager et al. (1986))	USA	M	16	<1	No
16	Humble et al. (1987)	USA	F	20	1.80	No
			M	8	>1.80	No

[a] Among never smoking subjects
[b] Yes = significant at 95% confidence level in comparison of exposed and non-exposed subjects; (Yes) = significance only in trend analysis or in subjects exposed to heavy smokers

association, it is not at all clear that it represents a causal effect of exposure to environmental tobacco smoke.

Before coming to any conclusion it is necessary to consider two important questions:

(a) Is the magnitude of the association plausible, in view of what is known about the epidemiology of active smoking and the relative levels of smoke constituents to which smokers and non-smokers are exposed?

(b) Is the epidemiological evidence open to any serious bias which might affect relative risk estimates in specific studies, or generally?

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Table 2. Comparison of relative risks of lung cancer in relation to passive and active smoking

Study number	Authors	Sex	Relative risk		Ratio of excess risk
			Passive	Active	
1	Hirayama (1981, 1984)	F	1.63	3.81	0.22
		M	2.25	4.91	0.32
3	Gillis et al. (1984)	F	1.00	1.53	0.00
		M	3.25	5.92	0.46
4	Trichopoulos et al. (1981, 1983)	F	2.08	2.90	0.57
5	Chan and Fung (1982)	F	0.75	3.07	−0.12
6	Correa et al. (1983)	F	2.07	18.51	0.06
		M	2.00	18.27	0.06
7	Buffler et al. (1984)	F	0.78	5.37	−0.05
		M	0.52	5.26	−0.11
9	Koo et al. (1984, 1987)	F	1.64	3.80	0.23
11	Akiba et al. (1986)	F	1.50	3.36	0.21
		M	1.80	3.55	0.31
12	Lee et al. (1986)	F	1.00	4.75	0.00
		M	1.30	12.91	0.03
14	Wu et al. (1985)	F	1.20	4.50	0.06

Plausibility

Table 2 compares relative risks of lung cancer in relation to passive and active smoking. The passive smoking estimates compare risk in never smokers according to whether or not they are married to a smoker, while the active smoking estimates compare ever smokers and never smokers. Exceptionally, in studies 1 and 3, the comparison is in relation to current rather than ever smoking. The table also shows the ratio of excess risk in relation to passive and active smoking. Nine of the 16 ratios suggest an effect of passive smoking 6% or less than that of active smoking, while seven suggest an effect 20% or more. Overall the epidemiological data appear to be indicating that passive smoking has 10–15% of the effect of active smoking. Most studies of active smoking suggest a linear relationship between lung cancer risk and number of cigarettes smoked per day, though a quadratic relationship has been proposed (Doll and Peto 1978). It follows that if the epidemiological data are unbiased one would expect that the average dose received from passive smoking is at least 10%–15% of that from active smoking.

Many workers have used the (virtually) tobacco specific marker cotinine as an indicator of exposure of passive and active smokers. Table 3, based on an extensive UK study by Lee (1987) which will be referred to in more detail below, found that the increase in salivary cotinine in relation to passive smoking was less than 1% of that in relation to active smoking. Similar findings have been reported by other workers (e.g. Jarvis et al. 1984). The only study reporting relative levels much higher than this (Matsukura et al. 1984) has been questioned (Adlkofer et al. 1985; Pittenger 1985).

Since lung cancer risk in smokers is generally thought to be related to particulate matter rather than nicotine, it can be argued that an index of relative exposure of passive

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Table 3. Salivary cotinine levels in relation to active and passive smoking

Exposure	Sex	Salivary cotinine (ng/ml)		
		Exposed	Non-exposed	Differences
Active smoking	M	319.2	0.85	318.3
	F	310.6	0.40	310.2
Spouse smoking (among non-smokers)	M	2.9	0.6	2.3
	F	1.0	0.3	0.7
Ratio of differences		Male 0.7%		
		Female 0.2%		

Table 4. Smoking related particulate levels in US smokers and non-smokers

Measure	Sex	Smoking related particulates (mg/day)		
		Active smoker	Non-smoker	Ratio
Inhaled dose	M	477.3	0.63	0.1%
	F	366.5	0.30	0.1%
Retention		80%	11%	
Retained dose	M	381.8	0.069	0.02%
	F	293.2	0.033	0.01%

and active smokers based on particulate matter would be more relevant. Table 4, based on Arundel et al. (1986), gives estimates for the US population of relative inhaled and retained particulate matter doses of non-smokers and active smokers. The ratios in Table 4 have to be adjusted upwards by a factor of 2 or 3 to make them comparable with the data in Tables 2 and 3, since (see Table 3) the difference between exposed and non-exposed non-smokers is two to three times the average level of non-smokers. This brings the inhaled dose estimates broadly in line with the cotinine estimates, though the retained dose estimates are about an order of magnitude lower. The lower figure for retained particulate matter is based on the work of Hiller et al. (1982a,b) who found that the collection efficiency of particles in environmental tobacco smoke is 11%, in contrast to the substantially higher figure of 80% for mainstream smoke. Robins (1986) also calculated that non-smokers take in the equivalent of an extremely small number of cigarettes per day in terms of respirable particulates. He noted that estimates of cigarette equivalents based on cotinine may be misleadingly high, since, whereas nicotine is in the particulate phase in mainstream smoke and will be absorbed mainly through the lungs, nicotine in ETS is mainly in the vapour phase, and, being water soluble, can be absorbed through the mucous membranes without ever reaching the lungs.

There appears to be a *huge discrepancy*, of two or perhaps three orders of magnitude between the claimed relative effects of passive and active smoke exposure and the much smaller relative exposure of passive and active smokers. What might explain this huge discrepancy?

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One might argue that studies of active smoking, by including exposed and non-exposed non-smokers in their comparison group, underestimate the effect of active smoking so that the ratios in Table 2 are too high.

This is irrelevant for three reasons:

(a) the comparison between Tables 2 and 3 is in fact direct and not affected by this false baseline problem,
(b) failure to take the false baseline into account would have virtually no effect if risk was proportional to exposure and exposures in passive smokers are so low and
(c) it ignores a bias in the opposite direction due to failure to take into account the fact that smokers obviously have greater passive smoke exposure than do non-smokers.

Another point to be considered is duration of smoking. Since, in active smokers, risk of lung cancer is approximately related to the 4th power of duration of smoking (Doll and Peto 1978), one might infer that failure to take account of differences in duration might cause relative bias by a factor of 3.2 ($= 60_4/45_4$) when comparing a 60 year old non-smoker exposed to passive smoke from birth and a 60 year smoker who started at age 15. Actually, the relative bias will be much less than this for two reasons. First, by no means all passive smokers will have been exposed since birth. Second, the "duration to a power" formula is only a valid approximation at smoker doses. Assuming a multistage model, it can easily be shown that at low doses the excess risk in relation to passive smoking becomes approximately linearly related to duration of smoking.

Neither of the above points really affect the huge discrepancy for which an explanation is being sought. If one is still wishing to accept the epidemiology as valid, one would have to seek an explanation either in a greater toxicity of ETS than mainstream smoke or in a greater susceptibility of non-smokers. While there is evidence that sidestream smoke has higher concentrations of some toxic chemicals than mainstream smoke, the relevance of this finding to environmental tobacco smoke which is aged, vastly diluted, chemically altered sidestream smoke, is not at all clear. There does not appear to be any direct evidence that ETS is particularly noxious. Nor is there any direct evidence that active smoking reduces susceptibility to relevant effects of ETS.

Limitations of Epidemiology

While it is not possible to completely rule out such explanations, the obvious alternative explanation – that the epidemiology is in some way biassed – seems on the face of it much more plausible. While the claimed effect of passive smoking may be large when viewed against the magnitude of effect predicted on dosimetric grounds, it is actually quite small when viewed against the magnitude of effect it has proved possible in the past to reliably identify using epidemiological methods. Alderson (1983) has suggested that a well designed case-control study should be able to confirm a two fold difference in risk but that, for differences less than this, the power of the study design may be inadequate. While case-control studies are particularly susceptible to a variety of sources of potential bias, this conclusion may well be true for any non-randomised epidemiological study (Lee 1988a).

In trying to assess whether bias might have arisen in the epidemiological evidence it is necessary to consider potential limitations of the available data. A number of general points can be made:

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Unrepresentativeness

Although it is clear that the combined study population in Table 1 is not fully representative of non-smokers, this does not appear to be a serious issue, since studies have been carried out in the US, UK, Greece, Sweden, Japan and Hong Kong, and Wald et al. (1986) found no evidence of significant heterogeneity of relative risk estimates.

Sample Size

While none of the studies considered in Table 1 concern particularly large numbers of non-smokers with lung cancer, chance can hardly be the total explanation of the association between passive smoking and lung cancer since the overall relative risk estimate quoted by Wald et al. (1986) of 1.35 is quite highly statistically significant, with 95% confidence limits of 1.19–1.54.

Confounding

Not all the studies considered have taken into account the possible confounding effect of factors known or suspected to be related to lung cancer, such as occupation or nutrition. Although it would perhaps be expected that non-smokers married to smokers might to some extent share the tendency of smokers to work in dirtier jobs, standardisation for occupation, or indeed any confounding factor, has never been found in practice to explain any material part of the association between lung cancer and passive smoking. It does not seem likely that failure to take confounding factors into account has materially affected the issue.

Inappropriate Choice of Controls

General scientific principles demand that like should be compared with like as far as possible. In a number of studies, there were clear exceptions to this. One example is the study of Trichopoulos et al. (1981, 1984) in which controls came from a different hospital. This may cause bias if patients came from different catchment areas with different smoking characteristics. Another example is the recently reported study of Humble et al. (1987), in which virtually all the interviews with controls were conducted directly while much of the data for cases came from surrogates. While inappropriate choice of controls may have materially biassed a few studies, it does not seem very likely, however, that it is a major explanation for the huge discrepancy.

Inaccuracy of Disease Classification

It is well known that diagnosis of lung cancer is imperfect and studies such as those by Garfinkel et al. (1985) which took pains to check and review all available evidence are to be preferred to those that did not do so. However, random misclassification of diagnosis would be expected to reduce the observed association between lung cancer and passive smoking, not increase it, and differential misclassification of diagnosis does not seem very likely, inasmuch as the doctor making the diagnosis is likely to have been blind to the

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patient's ETS exposure in most cases, and not to have been affected by it even if he was, given most diagnoses were made before the first study on the issue was published in 1981.

Non-reporting Bias

A problem in combining results from various studies to come to an overall assessment of the evidence, by so-called "meta-analysis", is the possibility that the studies being combined are not representative of all those that have been carried out. In particular, overall estimates of relative risk may be biassed upward if a scientist is less likely to submit for publication, or a journal is less likely to publish, studies which show no significant relationship of disease to the factor of interest or a significant trend in the direction opposite to that expected in advance. Convincing evidence of bias resulting from this in the context of randomised controlled trials has recently been collected by Chalmers et al. (1987) and the problem may generally be greater in epidemiological studies. One can easily imagine an investigator running a range of statistical analyses, finding a few significant associations of interest, and then publishing papers on those, ignoring the non-significant relationships. One can also imagine journals not being too keen to given space to a paper on a new null association and one must inevitably wonder whether the reason the first two studies published on passive smoking and lung cancer (Hirayama 1981; Trichopoulos 1981) found a significant association was because first published papers on any association tend to be positive. Indeed, there seems a case for carrying out meta-analysis giving most weight to studies showing no association and least weight to studies published first.

Although it is obviously important to conduct research into the problems of non-reporting bias in epidemiological studies, it is difficult to claim that it is the full explanation of the overall association between passive smoking and lung cancer. The reasons for this view are two-fold. Firstly, the overall association remains significant (though the relative risk estimate reduces to 1.20), even after eliminating the Hirayama and Trichopoulos results. Secondly, the fact that lung cancer and passive smoking has been a very "hot" issue in recent years suggests researchers should now be able to publish results from studies showing no association between passive smoking and lung cancer risk.

Lack of Objective Measure of ETS Exposure

A limitation of all the published epidemiological evidence is lack of objective measurement of exposure to ETS. Subjects are classified mainly by whether or not they are married to a smoker and occasionally by reported degree of exposure outside the home, but there are no data available either on ambient levels of tobacco smoke constituents at home or at work or on levels in body fluids such as blood, urine or saliva. While (e.g. see Table 3) it can be shown that marriage to a smoker is indeed associated with increased levels of cotinine, the relatively crude method used for determining exposure leads to possibilities of bias in case-control studies where knowledge of disease may consciously or subconsciously affect reporting of ETS exposure. While this may have caused upward bias of the reported relative risk in some case-control studies, it can hardly explain the whole association, since it would not be expected to cause upward bias in prospective studies and the association seems as strong in prospective as in case-control studies.

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Table 5. Hypothetical example of bias due to misclassification of 5% of smoking subjects as non-smokers

Smoking habit*		Assumed		Observed			
Subject	Spouse	N	Risk	N	Risk	Passive effect	Active effect
NS	NS	60	1	60 + 2 = 62	1.61	1	
NS	S	40	1	40 + 3 = 43	2.33	1.44	
NS	Total	100	1	100 + 5 = 105	1.90		1
S	NS	40	20	40 − 2 = 38	20		
S	S	60	20	60 − 3 = 57	20		
NS	Total	100	20	100 − 5 = 95	10		10.5

Assumed concordance = (60 × 60)/(40 × 40) = 2.25
Observed concordance = (62 × 57)/(43 × 38) = 2.16

* NS, non-smoker; S, smoker

Lack of Objective Measure of Active Smoking Status

Although considered last, this appears to be the most serious problem affecting the epidemiological evidence on passive smoking and lung cancer. As will be shown in the next section, completely erroneous conclusions can be reached when the "non-smokers" being studied actually include a small proportion of misclassified true smokers.

Misclassification of Active Smoking Habits as a Major Source of Bias

As shown in Table 5, misclassification of a small proportion of smokers as non-smokers, coupled with a tendency for smokers to be married to smokers ("concordance") can create an apparent positive effect of passive smoking when no actual effect exists. It also leads to an underestimation of the active smoking effect and of the concordance. The passive smoking bias depends critically on the assumed relative risk for active smoking, the degree of concordance and on the level of misclassification of subject smokers as non-smokers. This source of bias will also produce an artificial dose response relationship when the "non-smoking" subjects are divided according to the amount smoked by the spouse. It can be shown (Lee 1988b) that misclassification of non-smoking subjects as smokers and of smoking spouses as non-smokers causes a degree of bias that is minor compared with that resulting from misclassification of smoking subjects as non-smokers.

In an attempt to determine the extent to which smokers misreported their smoking habits and to which smokers tend to be married to smokers, Lee (1987) carried out three separate studies. In the first study, which concerned accuracy of reported current habits, 1775 British subjects were asked about their smoking habits and use of other nicotine products in a non-health context likely to minimize underreporting of smoking. They were then (with no prior warning) asked to provide saliva for cotinine analysis and 1537 agreed to do so. As shown in Table 3 there was in general a very marked difference between the cotinine levels of tobacco users and non-users. Using 30 ng/ml as a cut-off,

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1.1% of self-reported non-users could be classified as occasional users, with levels of to 100 ng/ml, while 1.4% could be classified regular users, with levels above 100 ng/ml.

The second study, which aimed at obtaining information, on accuracy of past smoking habits, followed up in 1985 540 subjects previously interviewed in 1980 about their smoking habits. Ten% claiming on one occasion never to have smoked made inconsistent statements on the other occasion, with inconsistent smokers being more often men, old, smokers of fewer cigarettes and long term ex-smokers.

The third study, which aimed at obtaining information on smoking habit concordance, involved 8857 subjects aged 16+ interviewed regarding their own smoking habits and that of their spouse. The concordance ratio, 3.55 in men and 3.07 in women, was found to be rather greater than that assumed in the example in Table 5. Concordance rose with amount smoked. Thus, the chance of having a spouse who was a manufactured cigarette smoker was 22% for subjects who reported no such smoking, and 45%, 52% and 59% respectively for subjects who reported smoking 1–17, 18–22 and 23+ manufactured cigarettes per day.

From the data obtained, Lee (1987) concluded that misclassification could bias relative risk estimates in relation to passive smoking upwards by a factor of 1.31 in men and 1.24 in women, not significantly different from the pooled estimate of risk in relation to passive smoke exposure.

At about the same time as Lee presented his findings, Wald et al. (1986) used similar techniques to estimate the bias from misclassification, but based on a number of smaller, and less representative studies, not specifically designed for the purpose. They estimated this misclassification would have less effect, reducing the pooled estimate of risk only from 1.35 to 1.30, i.e. it had only caused upward bias by a factor of 1.04.

Examination of the detail of how the estimates of bias of Wald et al (1986) and of Lee (1987) were arrived at reveals three reasons for the difference. The first was that Wald et al. (1986) used an assumed relative risk of 8 for the effect of active smoking observed in women whereas Lee (1987) used 10. The second was that the calculations of bias by Wald et al. (1986) were mathematically inaccurate, due to confusion between true relative risks in relation to active smoking and those observed (which are affected by misclassification). These are less important than the third reason, which is that Lee et al. (1987) found that 1.4% (10/808) self-reported non-smokers were current regular smokers, whereas Wald et al. (1986) only found 0.14% (1/705) such cases.

In an attempt to reconcile this difference, I have recently conducted a detailed literature review of the evidence on misclassification of smoking habits, which will be published as a book early in 1988.

Despite the various study designs and populations involved a number of clear conclusions were reached:

(1) Even in circumstances that are apparently similar quite a wide variation in the extent of misclassification can be found.
(2) The proportion of "non-smokers" subsequently found actually to be smokers is markedly higher in smoking cessation studies than in studies where the respondent is under no special pressure not to smoke.
(3) The proportion of "non-smokers" subsequently found actually to be smokers is also markedly higher in lung cancer patients than in the general population. This is not surprising in view of the overall *a priori* expectation that a lung cancer patient actually is a smoker.
(4) Studies of "non-smokers" without lung cancer and under no special pressure not to smoke suggest that around 4% are likely actually to be current smokers. While not all

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studies provide information on the extent to which such misclassified smokers smoke, and those that do indicate many of them are occasional smokers, it seems that 1 to 2% of self-reported non-smokers are regular smokers.

(5) In addition to these misclassified current smokers there are a somewhat larger number of ex-smokers misclassified as never smokers. Available information suggests that these tend to have smoked less and a longer time ago than average ex-smokers.

(6) None of the studies have investigated whether the extent to which smokers deny smoking depends on whether their spouse happens to smoke, which is of theoretical importance as it could materially affect estimates of bias.

(7) There is even now virtually no information on the extent to which smoking habits might be misclassified in Japan and Greece, from whence came the early epidemiological evidence on passive smoking and lung cancer. The only study in Japan, by Akiba et al. (1986), provided data suggestive of substantial misclassification of smoking habits. Here, of 187 men who reported not smoking in 1964–68, as many as 96 (51%) reported in 1982 that they had smoked.

While there is an obvious need for further research on misclassification of smoking habits the results of the review[1] suggested strongly that Wald et al. (1986) had seriously underestimated its importance.

Overall Conclusion

It has clearly been shown that there is a huge discrepancy between the relative doses of smoke constituents to which passive and active smokers are exposed and the much larger relative effect claimed from epidemiological evidence. The most likely explanation for this discrepancy seems to be a persistent bias affecting all the studies due to a small proportion of smokers being wrongly classified as non-smokers in the epidemiological studies.

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[1] Supported by a recent large study by Coultas et al. (American Review of Respiratory Diseases, 1987, 136, 305–309) who found 63 subjects with salivary cotinine ≥ 20 ng/ml among a sample of 1,360 New Mexicans reporting they were not current smokers.

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An Introduction to the Study of Smoking Using Urinary Hydroxyproline

H. Kasuga

Summary

The indicators used to identify the effects of environmental tobacco smoke (ETS) and exposure to low level nitrogen dioxide (NO_2) on the respiratory system are so weak that they can not be detected using traditional markers such as the increased prevalence of respiratory symptoms and a decrease in lung function. After studying urinary hydroxyproline (HOP) starting in 1977, we first reported the significant relationship between HOP and smoking, ETS and NO_2 in the air, in 1981. Since then, the coherent association between urinary HOP and the established pathological and biological development of lung diseases has been studied. Bias problems based on confounding factors, misclassification of nonsmokers and over- or underestimation of ETS effects also have been discussed.

Among articles presented by us during the past 4 years, several papers and some arguments for and against this study on urinary HOP were introduced:

1) The effect of cessation from smoking on the urinary excretion of hydroxyproline [19].
2) A prospective repeated cross-sectional study on the possible health effects caused by automobile exhaust and passive smoking [20].
3) Impact of smoking on the concentration and activity of alpha-1-antitripsin in serum, in relation to the urinary excretion of hydroxyproline. Matsuki H, Kasuga H et al., 1988.
4) Behavior of urinary hydroxyproline and effect of cigarette smoking in silicosis. Osaka F, Kasuga H, Matsuki H et al., 1985.
5) Opinions contrary to the relationship between urinary hydroxyproline and smoking, ETS and NO_2.

Introduction

Hydroxyproline (HOP) is one of the essential constituents in collagen and elastine and is an unique one which is not found in other tissues. Therefore, urinary HOP is regarded to be a potential candidate for the study of the breakdown of lung tissue due to smoking and environmental tobacco smoke (ETS).

As is generally known, the index symptom such as "a persistent cough and phlegm" based on the BMRC Questionnaire [1] is used frequently as a clinical marker, but it is not applicable for ETS effects because prevailing concentrations of ETS are estimated to be less than 1% of an undiluted mixture of sidestream and second-hand mainstream smoke. Therefore, urinary HOP as a biochemical marker for ETS effects appeared on the stage, and a causal relationship between smoking including ETS and its health effect was

H. Kasuga (Ed.) Indoor Air Quality
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